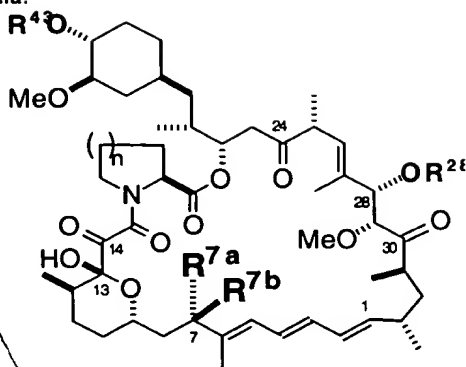


Claims:

1. A compound of the formula:

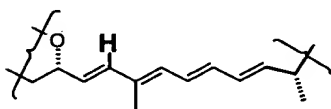


wherein

n is 1 or 2;

R28 and **R43** are independently selected from the group consisting of H and a substituted or unsubstituted aliphatic or acyl moiety;

one of **R7a** and **R7b** is H and the other is halo, **-RA**, **-ORA**, **-SRA**, **-OC(O)RA**, **-OC(O)NRARB**, **-NRARB**, **-NRBC(O)RA**, **-NRBC(O)ORA**, **-NRBSO2RA** or **-NRBSO2NRARB'**; or **R7a** and **R7b**, taken together, are H in the tetraene moiety:



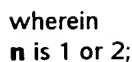
where **RA** is H or a substituted or unsubstituted aliphatic, heteroaliphatic, aryl, or heteroaryl moiety

and where **RB** is H, OH or a substituted or unsubstituted aliphatic, heteroaliphatic, aryl, or heteroaryl moiety;

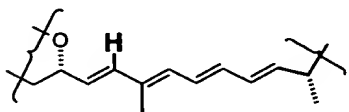
as a substantially pure stereoisomer or mixture of stereoisomers, and as a pharmaceutically acceptable derivative thereof.

2. The compound of claim 1 wherein **n** is 2.
3. The compound of claim 1 or 2 wherein **R7a** is -OMe and **R7b** is H.
4. The compound of any of claims 1-3 wherein **R28** is H.
5. The compound of any of claims 1-4 wherein **R43** is H.
6. The compound of any of claims 1, 2, 4 or 5 wherein either **R7a** is a moiety other than -OMe or **R7b** is a moiety other than H.
7. The compound of claim 6 wherein one of **R7a** and **R7b** is **-NRBC(O)RA**, **-NRBC(O)ORA**, **-NRBSO2RA** or **-NRBSO2NRARB'**.

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one of **R7a** and **R7b** is H and the other is halo, -**RA**, -**ORA**, -**SRA**, -**OC(O)RA**, -**OC(O)NRAR^B**, -**NRAR^B**, -**NRBC(O)RA**, -**NRBC(O)ORA**, -**NRBSO₂RA** or -**NRBSO₂NRAR^B**; or **R7a** and **R7b**, taken together, are H in the tetraene moiety:



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where **RA** is H or a substituted or unsubstituted aliphatic, heteroaliphatic, aryl, or heteroaryl moiety and where **RB** is H, OH or a substituted or unsubstituted aliphatic, heteroaliphatic, aryl, or heteroaryl moiety;

as a substantially pure stereoisomer or mixture of stereoisomers, and as a pharmaceutically acceptable derivative thereof.

21. The compound of claim 20 wherein n is 2.

21 The compound of claim 20 or 21 in which -OR⁴³ is in the S orientation.

23 The compound of claim 20 or 21 in which -OR⁴³ is in the R orientation.

24. The compound of any of claims 20-24 wherein **R^{7a}** is -OMe and **R^{7b}** is H.

25. The compound of any of claims 20 - 24 wherein **R²⁸** is H.

26. The compound of any of claims 20 - 25 wherein **R⁴³** is H.

27. The compound of any of claims 20-23 or 25-26 wherein either **R^{7a}** is a moiety other than -OMe or **R^{7b}** is a moiety other than H.

28. The compound of claim 27 wherein one of **R^{7a}** and **R^{7b}** is -NR^BC(O)RA, -NR^BC(O)ORA, -NR^BSO₂RA or -NR^BSO₂NRAR^{B'}.

29. The compound of claim 28 in which **RB** is H, OH or alkyl.

30. The compound of any of claims 20-25 or 27-29 wherein **R⁴³** is an aliphatic moiety.

31. The compound of claim 30 wherein the aliphatic moiety is optionally substituted alkyl moiety.

32. The compound of claim 31 wherein the alkyl moiety is a hydroxyalkyl moiety.

33. The compound of claim 30 wherein the aliphatic moiety is an optionally substituted alkenyl moiety.

34. The compound of claim 33 wherein the alkenyl moiety is an allyl or substituted allyl group.

35. The compound of any of claims 20-25 or 27-29 wherein **R⁴³** is an acyl moiety.

36. The compound of claim 35 wherein **R⁴³** is a substituted acyl moiety.

37. The compound of claim 36 wherein **R⁴³** is an acyl moiety of the formula RAR^BN-alkyl-C(O)-.

38. The compound of claim 26, wherein **R²⁸** and **R⁴³** are H, **R^{7a}** is OMe, and **R^{7b}** is H.

39. The compound of claim 27 - 29 wherein n is 2, **R²⁸** and **R⁴³** are H.

40. The compound of any of claims 30-39 wherein n is 2, **R²⁸** is H, **R^{7a}** is -OMe and **R^{7b}** is H.

41. A composition comprising a compound of any of claims 1 - 40 and one or more pharmaceutically acceptable carriers, diluents or excipients.

42. A method for epimerizing the hydroxy group of an aldol moiety which comprises contacting a compound containing an aldol moiety with a titanium tetraalkoxide reagent under suitable conditions and for a sufficient time to permit epimerization.

43. The method of claim 42 wherein the titanium tetraalkoxide reagent is titanium tetraisopropoxide.

44. The method of claims 42 or 43 which further comprises recovering the epimerized product.

45. The method of any of claims 42-44 wherein the aldol-containing compound is rapamycin or a rapamycin derivative or analog.

46. A method for multimerizing chimeric proteins in cells which comprises:

(a) providing cells which contain:

(i) a first recombinant nucleic acid encoding a first chimeric protein which binds to rapamycin or a derivative thereof and which comprises at least one FKBP domain and at least one protein domain heterologous thereto, wherein the FKBP domain comprises a peptide sequence selected from:

- (1) a naturally occurring FKBP
- (2) a variant of a naturally occurring FKBP in which up to 10 amino acid residues have been deleted, inserted, or replaced with substitute amino acids,
- (3) an FKBP encoded by a DNA sequence capable of selectively hybridizing to a DNA sequence encoding an FKBP of (i) or (ii);

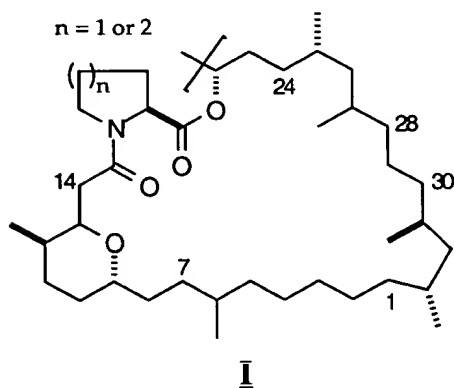
(ii) a second recombinant nucleic acid encoding a second chimeric protein which forms a complex with both (a) rapamycin or a rapamycin analog and (b) the first chimeric protein, and which comprises at least one FRB domain and at least one domain heterologous thereto, wherein the FRB domain comprises a peptide sequence selected from:

- (1) a naturally occurring FRB domain,
- (2) a variant of a naturally FRB domain in which up to 10 amino acid residues have been deleted, inserted, or replaced with substitute amino acids,
- (3) an FRB domain encoded by a DNA sequence capable of selectively hybridizing to a DNA sequence encoding an FRB of (iv) or (v);

and

(b) contacting the cells with a 28-epirapalog which forms a complex containing itself and at least one molecule of each of the first and second chimeric proteins,

where the 28-epirapalog has an immunosuppressive effect less than 0.01 times that of rapamycin and comprises the substructure of formula I:



bearing one or more optional substituents, optionally unsaturated at one or more carbon-carbon bonds spanning carbons 1 through 8, as a substantially pure stereoisomer or mixture of stereoisomers, or a pharmaceutically acceptable derivative thereof.

47. A method for multimerizing chimeric proteins in cells which comprises:

(a) providing cells which contain:

(i) a first recombinant nucleic acid encoding a first chimeric protein which binds to rapamycin or an analog thereof and which comprises at least one FKBP domain and at least one protein domain heterologous thereto, wherein the FKBP domain comprises a peptide sequence selected from:

- (1) a naturally occurring FKBP
- (2) a variant of a naturally occurring FKBP in which up to 10 amino acid residues have been deleted, inserted, or replaced with substitute amino acids,
- (3) an FKBP encoded by a DNA sequence capable of selectively hybridizing to a DNA sequence encoding an FKBP of (i) or (ii);

(ii) a second recombinant nucleic acid encoding a second chimeric protein which forms a complex with both (a) rapamycin or a rapamycin analog and (b) the first chimeric protein, and which

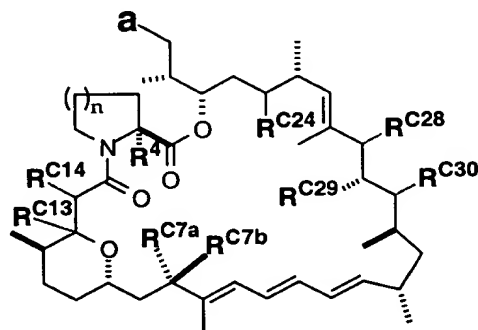
comprises at least one FRB domain and at least one domain heterologous thereto, wherein the FRB domain comprises a peptide sequence selected from:

- (1) a naturally occurring FRB domain,
- (2) a variant of a naturally FRB domain in which up to 10 amino acid residues have been deleted, inserted, or replaced with substitute amino acids,
- (3) an FRB domain encoded by a DNA sequence capable of selectively hybridizing to a DNA sequence encoding an FRB of (iv) or (v);

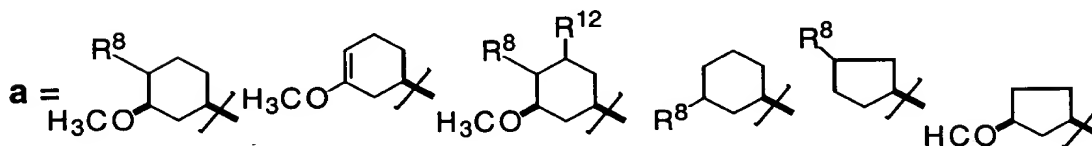
and

(b) contacting the cells with a 28-epirapalog which forms a complex containing itself and at least one molecule of each of the first and second chimeric proteins,

where the 28-epirapalog is of the formula:



wherein



one of **RC7a** and **RC7b** is H and the other is -H, halo, -R², -OR¹, -SR¹, -OC(O)R¹, -OC(O)NHR¹, -NHR¹, -NHR¹R², -NHC(O)R¹, or -NH-SO₂-R¹, where R² = aliphatic, heteroaliphatic, aryl, heteroaryl or alkylaryl,

RC30 is halo, -OR³ or (=O),

RC24 is =O, =NR⁴, =NOR⁴ or =NNHR⁴, -NHOR⁴ or -NHNHR⁴, -OR⁴, -OC(O)R⁴, -OC(O)NR⁴, halo or -H,

RC14 is =O, -OR⁶, -NR⁶, -H, -NC(O)R⁶, -OC(O)R⁶ or -OC(O)NR⁶

RC30 is H, -R⁷, -C(O)R⁷ or -C(O)NHR⁷ or a cyclic moiety bridging C28 and C30

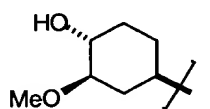
RC28 is halo or -OR³

RC29 is H, OH or OMe

where each substituent is present in either stereochemical orientation unless otherwise indicated, and where **R1**, **R4**, **R5**, **R6**, **R7**, **R9**, **R10** and **R11** are independently selected from H, aliphatic, heteroaliphatic, aryl or heteroaryl;

R8 is H, halo, -CN, =O, -OH, -NR⁹R¹⁰, OSO₂CF₃, OSO₂F, OSO₂R^{4'}, OCOR^{4'}, OCONR^{4'}R^{5'}, or OCON(OR^{4'})R^{5'};

in which one or both of **RC13** and **RC28** is a halo substituent; both **RC24** and **RC30** are other than =O; one of **RC7a** and **RC7b** is H and the other is phenyl, di- or tri-substituted phenyl or a mono- or di-substituted heterocyclic moiety; n is 1; and/or moiety "a" is other than



as a substantially pure stereoisomer or mixture of stereoisomers, or a pharmaceutically acceptable derivative thereof.

48. The method of claim 47 wherein **RC13** is halo.

49. The method of claim 48 wherein **RC13** is fluoro.

50. The method of claim 47, 48 or 49 wherein **RC28** is halo.

51. The method of claim 50 wherein **RC28** is fluoro.

53. The method of claim 52 wherein one or both of RC²⁴ and RC³⁰ are -OH, -OR¹ or halo.

54. The method of any of claims 47 - 53 wherein at least one of RC7a and RC7b is a moiety other than -OMe.

55. The method of claim 54 wherein one of RC7^a and RC7^b is H and the other is phenyl, di- or tri-substituted phenyl or a mono- or di-substituted heterocyclic moiety.

56. The method of claim 54 wherein one of RC7^a and RC7^b is H and the other is o,p-dialkoxyphenyl or trialkoxyphenyl.

57. The method of claim 54 wherein one of R^{C7a} and R^{C7b} is H and the other is o,p-dimethoxyphenyl, o-methoxy-p-ethoxyphenyl, o-ethoxy-p-methoxyphenyl, o,p-diethoxyphenyl, trimethoxyphenyl or triethoxyphenyl.

58. The method of any of claims 46 - 57 wherein the 28-epirapalog has an immunosuppressive effect less than 0.01times that of rapamycin.

59. The method of any of claims 46 - 49, 51, 53 or 55 - 58 wherein the chimeric protein encoded by the first recombinant nucleic acid comprises at least one FKBP domain whose peptide sequence contains up to three amino acid replacements relative to a naturally occurring FKBP peptide sequence.

60. The method of claim 50 wherein the chimeric protein encoded by the first recombinant nucleic acid comprises at least one FKBP domain whose peptide sequence contains one amino acid replacement relative to a naturally occurring FKBP peptide sequence.

61. The method of claim 52 wherein the chimeric protein encoded by the first recombinant nucleic acid comprises at least one FKBP domain whose peptide sequence contains one amino acid replacement relative to a naturally occurring FKBP peptide sequence.

62. The method of claim 54 wherein the chimeric protein encoded by the first recombinant nucleic acid comprises at least one FKBP domain whose peptide sequence contains one amino acid replacement relative to a naturally occurring FKBP peptide sequence.

63. The method of claim 59 wherein the chimeric protein encoded by the first recombinant nucleic acid comprises at least one FKBP domain whose peptide sequence contains a replacement amino acid for Phenylalanine-36 of a naturally occurring FKBP peptide sequence.

64. The method of any of claims 60 - 63 wherein the chimeric protein encoded by the first recombinant nucleic acid comprises at least one FKBP domain whose peptide sequence contains a replacement amino acid for Phenylalanine-36 of a naturally occurring FKBP peptide sequence.

65. The method of any of claims 46 - 49, 51, 53, 55 - 58 or 60 - 63 wherein the chimeric protein encoded by the second recombinant nucleic acid comprises at least one FRB whose peptide sequence contains up to three amino acid replacements relative to a naturally occurring FRB peptide sequence.

66. The method of claim 50 wherein the chimeric protein encoded by the second recombinant nucleic acid comprises at least one FRB whose peptide sequence contains one amino acid replacement relative to a naturally occurring FRB peptide sequence.

67. The method of claim 52 wherein the chimeric protein encoded by the second recombinant nucleic acid comprises at least one FRB whose peptide sequence contains one amino acid replacement relative to a naturally occurring FRB peptide sequence.

68. The method of claim 54 wherein the chimeric protein encoded by the second recombinant nucleic acid comprises at least one FRB whose peptide sequence contains one amino acid replacement relative to a naturally occurring FRB peptide sequence.

69. The method of claim 59 wherein the chimeric protein encoded by the second recombinant nucleic acid comprises at least one FRB whose peptide sequence contains a replacement amino acid for one or more of Tyr2038, Phe2039, Thr2098, Gln2099, Trp2101 or Asp2102 in a naturally occurring FRB peptide sequence.

70. The method of any of claims 46-69 wherein at least one of the chimeric proteins comprises an action domain which is a DNA-binding domain, transcription activation domain or a cellular signaling domain for triggering growth, proliferation, differentiation or apoptosis upon dimerization with another protein containing at least one such signaling domain.

71. The method of any of claims 46 - 69 wherein the cells are grown in a culture medium and the contacting with a 28-epirapalog is effected by adding the 28-epirapalog to the culture medium.

72. The method of any of claims 46 - 69 wherein the cells are present in a whole organism and the contacting with a 28-epirapalog is effected by administering the 28-epirapalog to the organism.
73. The method of claim 72 wherein the cells are mammalian and the organism is a mammal.
74. The method of claim 73 wherein the cells are of primate origin and the organism is a primate.
75. The method of claim 74 wherein the primate is a human.
76. The method of any of claims 73 - 75 wherein the 28-epirapalog is administered orally.
77. A method for producing 28 epi, 29 epi, or 28,29 bis-epi compounds comprising the substructure of formula IV by subjecting a compound of formula IV to appropriate epimerizing conditions and recovering the desired epimer from the reaction mixture

